UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,566	04/02/2001	Peter W. Laird	47675-18	2853

22504 7590 05/31/2007
DAVIS WRIGHT TREMAINE, LLP
2600 CENTURY SQUARE
1501 FOURTH AVENUE
SEATTLE, WA 98101-1688

EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
05/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/825,566	LAIRD ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,8,11-17 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 6, 8, 11-17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1, 3, 6, 8, 11-17 and 19 are pending and under examination in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are newly applied, as necessitated by amendment. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

Withdrawn Rejections

2. The rejections maintained under 35 USC 102 and 103, in the previous office action, are withdrawn in view of the amendments to the claims.

3. The double patenting rejection is withdrawn in view of the amendments to the claims of the copending application.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

4. Claims 1, 3, 6, 8, 11-17 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims have been amended to recite "that extends from nucleotide 9843 to 10,043 of SEQ ID NO: 66, in step b of claim 1. The response cites the specification at page 7 line 35 to page 8 line 6, page 28, line 32, 33, and page 30 table II. The specification has been thoroughly reviewed but was not found to provide support for the claim amendment. Specifically, at page 8, line 1-2, the specification teaches that "CpG islands are typically, but not always, between about 0.2 to about 1kb". This does not provide specific support for the "length >200" found in appendix A. Notably, the specification acknowledges that CpG islands are not always this length, and also provides a minimum of "about .2", which does not provide specific support for a length of greater than 200, as the term "about" encompass a large genus of possible lower length limitations, and there is no specific teachings in the specification that provides for specifically, "length >200". Further, at page 28, the disclosure of "CpG:GpC ratio of 200 base pairs" does not provide support for greater than 200 as noted in Appendix A, nor do the primers of SEQ ID NOS 7 and 8 provide for the specific length of 201 bases highlighted in the appendix. Further, the specification provides no algorithm or equation which would allow the skilled artisan to only arrive at the specific fragments set forth in the appendix, nor does the appendix provide for any equation or algorithm which shows how the specific fragments listed were obtained, or where this equation or algorithm is supported in the specification. Accordingly, the amendment appears to have introduced new matter into the claimed invention.

5. Amended claims 1, 3, 6, 8, 11-17 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing or prognosing esophageal cancer, esophageal dysplasia, esophageal metaplasia, Barrett's intestinal

tissue, Barrett's esophagous, or combinations thereof comprising obtaining a sample of esophageal tissue comprising genomic DNA, performing a methylation assay of the tissue sample wherein the methylation assay determines the methylation state of the sequence of the MYOD1 gene delimited by the primer pair of SEQ ID NO: 7 and 8 as compared to a normal control DNA sample, and diagnosing or prognosing esophageal cancer, esophageal dysplasia, esophageal metaplasia, Barrett's intestinal tissue, Barrett's esophagous, or combinations thereof , based, at least in part, on the detection of hypermethylation of the sequence of the MYOD1 gene delimited by the primer pair of SEQ ID NO: 7 and 8 as compared to a normal control DNA sample, does not reasonably provide enablement for diagnosis or prognosis of esophageal cancer, esophageal dysplasia, esophageal metaplasia, Barrett's intestinal tissue, Barrett's esophagous, or combinations thereof, by detecting hypermethylation, or determining the hypermethylation state of, in 'at least one" CpG sequence in a CpG island or the island set forth in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are now broadly drawn to diagnosis or prognosis of esophageal cancer, esophageal dysplasia, esophageal metaplasia, Barrett's intestinal tissue, Barrett's esophagous, or combinations thereof by determining the hypermethylation state of "at least one" genomic CpG sequence in the MYOD1 gene CpG island sequence as set forth in claim 1. The claims encompass a method of making any diagnostic or prognostic prediction or determination of any esophageal cancer related condition by determining the hypermethylation state of a single genomic CpG sequence in a single CpG island.

The amount of direction or guidance and Presence and absence of working examples:

The specification teaches that CpG islands in the promoter region of the MYOD1 gene delimited by the primer pair of SEQ ID NO: 7 and 8 were hypermethylated in intestinal metaplasia tissue as compared to normal esophageal tissue (see page 36, lines 4-6). The specification teaches that increases in MYOD1 methylation were found in esophageal adenocarcinoma, Barrett's esophagus, and dysplasia (see Fig. 1). The specification further teaches that MYOD1 hypermethylation was correlated with increases in tumor stage (see Fig. 4, page 38). The specification is silent, however, with regard to any association between methylation of even a single CpG dinucleotide in a MYOD1 CpG island, and the diseases set forth in the claims. Such recitation, however, encompasses an association between the methylation status of a single CpG dinucleotide and diagnostic or prognostic significance. The specification teaches that aberrant hypermethylation in cancer cells often occurs at CpG islands (page 1). This finding, strongly corroborated by the teachings in the art, suggest that the

methylation of a single CpG island would not be predictably diagnostic or prognostic of any disease or disorder, let alone esophageal cancer, Barrett's intestinal tissue, Barrett's esophagous, esophageal metaplasia or dysplasia. CpG islands represent stretches of genomic DNA with a certain GC content, as defined by the specification. The specification provides an association between *hyper*methylation of CpG islands in the sequence of the MYOD1 gene delimited by the primer pair of SEQ ID NOS 7 and 8, however, the specification provides no predictable correlation that the methylation status of any single CpG dinucleotide in a single island in MYOD1, would be diagnostic or prognostic of any disease, let alone esophageal cancer or the other conditions encompassed by the claimed invention.

The state of the prior art and the predictability or unpredictability of the art:

In CACNAIG (see Toyota et al. Cancer Research, Vol. 59, pages 4535-4541, September 1999), a detailed analysis was provided for CpG islands within the gene. The eight regions were found to behave differently. For example Regions 1 and 2 behaved in a concordant manner. Region 3 had either no methylation or very low levels of methylation. Regions 4, 8 behaved differently and regions 5, 6, 7 behaved differently than regions 1-3. Thus, with regards to hypermethylation in cancer, the CpG region upstream of CACNAIG appears to behave independently (page 4538, col. 1).

The claims have been amended to encompass hypermethylation to any region within a CpG island ("a region flanked by SEQ ID NOS 4 and 5"), which broadly encompasses analysis of a single CpG within an island. However, the art does not appear to provide support that the methylation state of a single CpG sequence would be predictably diagnostic or prognostic of

cancer. For example, Pao (Pao et al; Human Molecular Genetics, Vol. 10, No. 9, pages 903-910) analyzed methylation of the CpG island in the promoter of EDNRB in normal and tumor cells. Pao teaches that 11 individual CpG sites located throughout the CpG island were analyzed and that specific sites with high methylation levels in several tumors were also methylated in normal tissues (abstract). Figure 2 illustrates the methylation profile in the promoter in primary tissue samples. Pao teaches that analysis of the 11 individual CpG sites spanning the whole island demonstrated that "several non-adjacent CpG sites showed high methylation in tumor tissues and some of the normal samples" (page 904, col. 1; first full para). Pao teaches that in normal tissues, increased methylation is found at CpG-130, the 5' most CpG dinucleotide, (page 905, col. 1). Pao further teaches that CpG 336 remained resistant to hypermethylation even when adjacent CpGs were highly methylated (page 906, col. 1, first para). Moreover Pao teaches that the findings showed that in the EDNRB 5' regulatory region, prostate, bladder and colon normal tissues have methylation patterns that are particular to each type of tissue (page 906, col. 1, first full par) and that some sites within the CpG island appeared to be preferential targets for de novo methylation whereas others seemed to be protected from hypermethylation changes.
Additionally, Cameron (Cameron et al; Blood, vol. 94, No. 7, pages 2445-2451, October 1999) teaches that methylation of the p15 CpG island is heterogeneous. Cameron teaches that there was marked heterogeneity for the specific CpG sites methylated (abstract). Cameron also teaches that the density of methylation within the CpG island and not any specific location correlated best with transcriptional loss (abstract). Cameron specifically teaches that some methylation assays are only capable of studying 2 to 4 CpG sites within an island and that it is therefore importance of hypermethylation at 1 or 2 CpG sites and their location relative to

transcription start sites remain to be determined (page 2445, col. 1, 2nd full para). Accordingly, the art at the time the invention was filed does not provide for a predictable correlation between the status of methylation of a single CpG as diagnostic or prognostic of tumor vs normal tissue. Additionally, the art does not appear to support that the individual sites in a particular island are predictably associated with each other dinucleotide in the island.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

Therefore, based on the limited guidance in the specification, and the unpredictability taught in the art, it would require undue experimentation for one of skill in the art to practice the invention as broadly as it is claimed. The specification does not appear to provide sufficient guidance to arrive at the CpG island set forth in the claim. The skilled artisan would have to screen a large number of patients to determine a predictable correlation between the "state of hypermethylation" of at least one genomic CpG sequence in a single CpG island of the MYOD1 gene was diagnostic or prognostic as broadly claimed. Based on the teachings of the art, this experimentation would require a large amount of unpredictable trial and error, which is considered undue. Based on the lack of guidance in the specification and the unpredictability taught in the art, undue experimentation would be required of the skilled artisan to practice the invention as broadly as it is claimed. Thus given the broad claims in an art whose nature is

identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

6. The response traverses the rejection. The response asserts at page 9, 2nd full para, that Toyota teaches that while different CpG islands within a gene area can behave differently or independently, the subregions within a larger CpG rich region "behave coordinately and define the behavior of the CpG island which comprises the subregions". This argument has been thoroughly reviewed but was found unpersuasive. Although Toyota teaches that the CpG rich region appears to be composed of two different islands, at page 4538 (col. 1, first full para), Toyota outlines the differences in methylation patterns between regions which appear to be within the same island. Additionally, the art of Pao and Cameron does not provide for a predictable correlation between the status of methylation of a single CpG as diagnostic or prognostic of tumor vs normal tissue and does not appear to support that the individual sites in a particular island are predictably associated with each other dinucleotide in the island.

The response's assertions with regard to the amendment to claim 1 to recite a particular island are not found persuasive for the reasons made of record in section 4 above. The specification does not appear to provide support for this amendment. Additionally, claims 3 and 8 continue to recite "corresponding" which does not appear to limit the primers to SEQ ID NOS 7 and 8 but appear to encompass other primers in the region. Additionally, it is not clear how a

single probe can delimit a region. The suggestion by the examiner of the term "delimited" was used to denote the area bounded by two sequences, that is SEQ 7 and 8, however the use of the term with a single probe appears to encompass any area that contains that probe. The rejection is therefor maintained.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-

0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton

Jehanne Sitton
Primary Examiner
Art Unit 1634
5/25/07